

# The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

NATIONAL INSTITUTES OF HEALTH ■ OFFICE OF THE DIRECTOR ■ VOLUME 8, ISSUE 5 ■ SEPTEMBER–OCTOBER 2000

## FROM THE GROUND UP: VRC TAKES ITS PLACE IN CAMPUS SKYLINE

by Fran Pollner

In May of 1997, President Clinton declared that an AIDS vaccine should be developed within 10 years and that a new research center at NIH would be the ticket to getting the job done.

Over the next few months, NIH marshalled intramural and extramural forces to conceptualize the height,



Almost ready for prime time, the Vaccine Research Center now stands tall between Building 49 (right—and actually across Convent Drive) and Building 37 (not shown).

breadth, and depth of this project—the dimensions, both physical and scientific, of what began as a “center without walls.” The resources to be amassed to generate AIDS vaccine candidates would be the bedrock as well for vaccine development in general. Scientists steeped in basic, translational, and clinical vaccine research would populate the labs. There would be on-site mini-vaccine-production facilities and off-site but nearby facilities for nonhuman primate studies.

The speed with which the “center without walls” materialized into the state-of-the-art, five-story Vaccine Research Center—essentially completed when the photo above was taken at *Catalyst* press time in September—matched the urgency of the need the VRC was created to address.

Construction was begun in the fall of 1998, and in the spring of 1999, *continued on page 11*

## WHERE TO DRAW THE BOTTOM LINE: FINANCIAL CONFLICT OF INTEREST IN CLINICAL RESEARCH

by Fran Pollner



*Steering the Course:* (left to right) FDA Commissioner Jane Henney; Ruth Kirschstein, NIH principal deputy director; and Stuart Nightingale, an HHS senior medical advisor and chair of the conference planning committee, set the stage for a two-day exploration of how best to disarm the threat of what Kirschstein termed a “collision” of financial interests and investigator objectivity.

One year after the death of 18-year-old Jesse Gelsinger in a University of Pennsylvania gene therapy trial, the research community and its federal overseers continue to grapple with strategies to ensure the scientific integrity of clinical trials, the safety of patients enrolled in them, and the objectivity of investigators conducting them.

These essential components of clinical research—scientific integrity, patient safety, and investigator objectivity—may be compromised when researchers or institutions conducting a trial, or members of the review board that approves it, are financially invested in the product under study or its sponsor, participants agreed at an overflow conference here on “Human Subject Protection and Financial Conflict of Interest.”

The conference was convened by HHS and its agencies (FDA, NIH, and CDC) to tackle the issue of real and perceived investigator bias in a research environment increasingly invested in “break-through” results and the drive for efficient technology transfer, as mandated in the Bayh-Dole Act.

The blurring lines between study spon-

sor and investigator and the ethical problems this creates—brought into sharp relief by the circumstances of the Penn trial but not unique to it—were the main subject of the conference. The spotlight was cast on the potential threats to study integrity wrought by the growing involvement of clinical investigators and research institutions in the companies sponsoring trials they are supervising.

The central questions posed to conference participants revolved around

*continued on page 4*

### CONTENTS

1 Conflict of Interest in Clinical Research	7 Research Postcards
VRC Materializes	8-9 PRAT Progress
2 From the DDIR: Volunteerism	10 Ombudsmanship
3 Catalytic Reactions/ Meetings	12-14 Recently Tenured
6 Summer Genetics Institute	15 Cartoon
	16 Catalytic Questions

## VOLUNTEERISM AMONG SCIENTISTS: PASSING THE TORCH



Michael Gottesman

The early career training of researchers rarely touches on one important aspect of collegiality and community among scientists. Researchers in training are expected to learn how to form and nurture scientific collaborations as part of their scientific activities. However, they do not usually hear about the important role that scientists play as volunteers. In addition to the many services that scientists provide within their own institutions, such as membership on tenure and search committees, critical volunteer services to the scientific community as a whole include reviewing papers and serving on editorial boards and review panels (such as NIH study sections) and as officers and board members of scientific societies. In general, these are activities that are not directly compensated, but are absolutely essential if the scientific enterprise is to prosper.

These volunteer activities form the infrastructure that supports the culture of science. Because scientists offer these services for free (or nearly free), it helps reduce the appearance of conflict of interest in decisions about manuscripts and grants. It also allows scientific societies to function more effectively, allowing them to focus on the goals of their members. Most scientists give freely of their time for these activities, and researchers in training should be taught, by word and deed, that volunteer activities on behalf of research are desirable and laudable.

Of course, volunteering has significant benefits, even if they are less tangible than financial remuneration. Academic promotions are based to some extent on recognition by fellow scientists, and participating in the kind of review activities listed above is viewed as a sign of such recognition. Scientists who volunteer for review groups influence publications and grant distribution and thus may ultimately affect the direction of a field, extending the reach of their intellectual activities beyond what could be achieved within one laboratory, or even a group of collaborating laboratories. For early

career researchers, assignment to an editorial board or a study section is frequently a chance to meet more senior colleagues and join a community of scientists. Finally, the personal satisfaction that comes from volunteering time and energy in support of science can be substantial.

For fellows, there is at least one conspicuous avenue for volunteer participation—service on the NIH Fellows' Committee and its projects. Run by Fellows for Fellows, this group has substantially improved the quality of life for early-career scientists at NIH. Over the course of the year, this group has many opportunities for volunteer participation—serving on review committees for the FARE awards and other projects, hosting speakers for the Wednesday Afternoon Lectures, and moderating their electronic bulletin board, as well as representing an institute on the committee itself.

Naturally, the amount of time one has to volunteer for such activities will depend on supervisors' approval and other pressing responsibilities. My intention here is to suggest that each of you strongly consider this use of at least some of whatever discretionary time you may find you have.

I may, of course, be preaching to the converted, for it seems to me

that scientists volunteer more of their time for activities in support of their profession than any other discipline. Many professional societies thrive thanks to the many members who serve as officers or on their various committees or on the editorial boards of the society's journals. But to ensure the continued vitality of biomedical research, senior researchers need to make one more contribution: We need to encourage our colleagues who are just beginning their research careers to consider volunteering some of their time for activities such as this. The public, and science, will benefit if we do.

—Michael Gottesman  
Deputy Director for Intramural Research  
(adapted from an article written for a professional society for which Gottesman volunteers)

THESE VOLUNTEER ACTIVITIES FORM THE INFRASTRUCTURE THAT SUPPORTS THE CULTURE OF SCIENCE. BECAUSE SCIENTISTS OFFER THESE SERVICES FOR FREE (OR NEARLY FREE), IT HELPS REDUCE THE APPEARANCE OF CONFLICT OF INTEREST IN DECISIONS ABOUT MANUSCRIPTS AND GRANTS. IT ALSO ALLOWS SCIENTIFIC SOCIETIES TO FUNCTION MORE EFFECTIVELY, ALLOWING THEM TO FOCUS ON THE GOALS OF THEIR MEMBERS.

## CATALYTIC REACTIONS

### On Expanding Programs For Graduate Students

I'm responding to the second question on the back page of the July-August 2000 issue on ways the new director of graduate program partnerships can improve and expand programs for graduate students.

The NICHD's National Center for Medical Rehabilitation Research (NCMRR) research initiatives include "training scientists for medical rehabilitation research." I would recommend that NIH support this goal by facilitating PhD-level training/fellowships between the Clinical Center (CC) Rehabilitation Medicine Department and programs such as the Rehabilitation Sciences program at University of Maryland and the developing Clinical Leadership program at George Washington University [in Washington, D.C.].

This type of arrangement may be supported in many ways such as work commitment/tuition reimbursement agreements (for intramural scientists) and laboratory rotations. Investing in the clinical research expertise of the CC staff and students/scientists from participating local universities would prove to honor the goals of NCMRR and benefit the patient and scientific community at large.

— Michael Harris-Love, CC

Dear Michael,

Your recommendation that NIH support PhD-level research training for clinical scientists is very appreciated. It strongly reflects the current thinking and a future goal of the Graduate Program Partnership Office (GPP).

The multi-institutional partnering model you envision for the MCMRR and universities is one rapidly emerging across the nation and world. As the GPP initiates new graduate training programs, we look to the leadership of the NIH faculty and fellows for their scientific direction and ideas.

The GPP looks forward to working with you and many others to move graduate training ideas into graduate degree programs.

—Mary DeLong, Ph.D.,  
Director, GPP

### Antiviral Drug Resistance

The HIV Drug Resistance Program (DRP) of the National Cancer Institute will hold its First HIV DRP Symposium, "Understanding Antiviral Drug Resistance," at the Westfields International Conference Center, Chantilly, Va., near Dulles Airport. The program begins with dinner Sunday, December 3, 2000, and closes after lunch Wednesday, December 6.

The symposium will assemble researchers who work in diverse viral systems yet share a common interest in mechanisms of antiviral drug action and resistance. Each session will focus on a different class of molecular targets for antiviral therapy, with emphasis on normal structure and function, interactions with antiviral drugs, and the evolutionary basis and specific mechanisms of viral resistance. For more information, see

<<http://web.ncicrf.gov/campus/symposium>>.

Early registration is encouraged. Contact symposium coordinator, Margaret Fanning, at 301-846-1995 or at <[fanningm@ncicrf.gov](mailto:fanningm@ncicrf.gov)> by November 10 to request assistance, assistive devices, or sign language interpretation. ■

### Women in Science Series

The annual seminar series of the Bethesda chapter of the Association of Women in Science—*Strategies for Success in Science*—announces the following 2000–2001 schedule.

**Tuesday, September 19**, "Exploring Bioinformatics Careers: Paths in the Neurosciences and Molecular Biology."

**Tuesday, October 31**, "A Report on the Status of Women Faculty in Science at MIT: An Update."

**Thursday, January 25**, "Employment Opportunities for Scientists at Other Federal Agencies."

**Tuesday, March 6**, "Science and Business: Working in Industry."

**Thursday, April 26**, "Career and Family: Challenges and Rewards."

All seminars are held in the Chapel at the Cloisters (Building 60). Light refreshments are available from 4:30 pm, and seminars usually start at 5:00 pm—except for October 31, when refreshments will be served at 3:30 pm and the presentation will begin at 4:00 pm. For more information, call Marion Zatz at 301-594-2379 or Mini Varughese at 800-446-0035. ■

### Disability Awareness: With a Focus on Ability

To showcase the skills and talents of 7.8 million workers with disabilities, two events will take place on the NIH campus in October in conjunction with "National Disability Employment Awareness Month."

The kick-off is Wednesday, October 4, with a fast and furious game of basketball played by 10 persons in wheelchairs. The NIH Police are challenging the Baltimore Ravens **Wheelchair Basketball Team!** Tip-off time is high noon on the Building 1 parking lot. Ruth Kirschstein, NIH principal deputy director, will throw the first jump ball. For those who can't make the noon game, another match is scheduled for later that evening in the Building 10 Gymnasium, on the 14th floor.

A **Disability Awareness Fair** will be held Tuesday, October 24, in the Building 10 Visitors Center, where national and local vendors will display disability-related resources and services from 11 am to 2:30 pm.

The objective is to highlight the benefits of tapping into the labor pool of persons with disabilities and provide practical information and resources about assistive technologies to NIH community.

For assistance or special accommodations, call Carlton Coleman, of OEO, at 496-2906. ■

## THE BOTTOM LINE

continued from page 1

where to draw the line between acceptable and unacceptable financial interests among the parties involved in a clinical trial and whether, when, and how much to disclose to study patients.

The answers were diverse. Many speakers believed that most financial conflicts of interest could be "managed" to eliminate the possibility of harm to either research subjects or research results. Others contended that nothing short of elimination of the financial conflict itself would do.

(Based on the conference proceedings and written responses to six questions posed in the July 3 *Federal Register* notice announcing the conference, HHS will produce new guidelines for the medical research community. The deadline for responses is September 30. See "Have Your Say," page 5.)

## Setting the Stage

"Objectivity," NIH Principal Deputy Director Ruth Kirschstein said, "lies at the heart of science and must not be compromised by financial gain—or fame or the pursuit of insights," she added, noting that it is not only money that can color an investigator's judgment, but that only money was the issue at hand this time around. She asked the assembled to "share your best practices" in the realms of disclosure of financial interest and distinguishing financial interests that do and do not compromise objectivity.

FDA Commissioner Jane Henney noted that under current FDA procedures, disclosure of an investigator's financial interest in the product under study—or certification that there are no such interests—is required at the time of FDA review of the completed study, not at the time of application to pursue the study. But she asked whether disclosure of financial interests alone would be enough to protect patient safety. The death of Jesse Gelsinger, she observed, had "raised the question of whether financial interest had clouded clinical judgment. . . . the multiple hats of the physician/clinical investigator/sponsor [create] real and perceived conflicts of interest and must be addressed."

## Zero Tolerance

The way to address conflicts of interest, according to Marcia Angell, a lecturer in social medicine at Harvard and former editor of the *New England Journal of Medicine*, is to prohibit them. She

defined a financial conflict of interest as any financial association that could cause an investigator to prefer one outcome over another and dismissed the notion that disclosure of financial conflicts of interest in patient consent forms would in any way protect patients. "That simply passes the buck to the patient. It's just 'caveat emptor.'"

Angell decried "dancing on the margins of the issue . . . to accommodate something that shouldn't exist in the first place" and pointed to Harvard's "impenetrable pages" as an example of "mind-boggling guidelines" that miss the essential point: "Investigators with grant support from industry must have no other financial ties to that company, just like a judge on the bench deciding the merits of a case."

"In my two decades [at the *NEJM*]," Angell said, "it has been my impression that bias in study design and interpretation of data are far more likely in investigators with industry ties."

Moreover, she advised that:

■ Grants from industry to institutions should come with no strings attached,

as they used to.

■ Technology transfer does not require consultancy fees.

■ Institutions and their senior officials should limit their investment portfolios to "rubies and racehorses."

"This might seem radical," she added, "but it's only because our society is so drenched in market ideology that opposition seems quixotic."

"It's a lot more complex than that," countered James Benson, an officer of the Advanced Medical Technology Association (formerly the Health Industry Manufacturers Association). Up to two-thirds of "breakthrough" devices, he said, originate from an engineer who creates a small start-up company and has no other way of financing research but through offering scientists equity.

Speakers for the Association of American Universities and the Association of American Medical Colleges cautioned



**Not Eye to Eye:**  
James Benson  
(left) and Marcia  
Angell

## The Wheels of Change

Much of the public examination of the conduct and federal oversight of the University of Pennsylvania gene therapy trial, as well as of clinical trials in general, has taken place on the NIH campus. Last December, newspapers across the country carried the details of how the Penn study was conducted, the pitfalls of adenovirus gene vectors, and the controversies over clinical trial adverse event reporting and the curtailed authority of the NIH Recombinant DNA Advisory Committee (RAC)—the substance of a heavily attended three-day meeting here of the RAC (see *The NIH Catalyst*, January-February 2000, page 1).

Subsequent meetings of the RAC and the Advisory Committee to the NIH Director (ACD) examined the boundaries of NIH and RAC oversight of clinical gene transfer research. An ACD working group convened last year by then-NIH director Harold Varmus issued a preliminary report in July suggesting changes in protocol submission and review procedures that would ensure RAC input into novel gene therapy protocols *before* they are presented to authorizing bodies such as the Food and Drug Administration. Although investigators would not be required to comply with any RAC requests, such as more preclinical work or protocol changes, they would be required to respond publicly. The overall effect of the ACD working group proposals would be, first, to ensure that no patient is enrolled in a gene transfer study that the RAC has not reviewed and, second, to make it more likely that RAC advice is followed. A majority of the working group, as well as the RAC itself, also opted to modify RAC requirements for the reporting of serious adverse events that occur in gene therapy trials to be more in line with those of the FDA, which requires immediate notification only of those serious adverse events that are both unexpected and related to the experimental therapy. A minority of the working group, however, urged that all serious adverse events be reported as they occur, and that a central body of experts, with both FDA and RAC presence, be established to receive and interpret these reports (see <<http://www.nih.gov/about/director/07122000.htm>>). NIH principal deputy director Ruth Kirschstein will act on the final ACD report.

Meanwhile, the NIH Intramural Research Program has crafted interim guidelines regarding reporting adverse events for intramural investigators involved in *any and all* clinical research. The details of these guidelines are under discussion, but the current requirement is expedited reporting to the IRB of all serious adverse events except those anticipated in the IRB-approved research protocol. ■

against overregulation and equating conflict of interest with scientific misconduct. The latter could be prevented with appropriate institutional safeguards.

### Industry Influence

Traditional sources of financial support for medical schools have been drying up, and industry has been stepping in. According to a survey undertaken by the Massachusetts General Hospital Institute for Health Policy, director David Blumenthal said, about 25 percent of medical school facilities have research support from industry and about 8 percent have equity in companies related to their research.



Sid Wolfe

Sid Wolfe, long-time director of the Washington-based Health Research Group, a patient advocacy organization, warned of the burgeoning "for-profit human experimentation industry" with its "business model of recruiting research subjects for their paying clients, the pharmaceutical companies." These corporations, he said, have no teaching or care responsibilities and they "recruit from private practices, offering monetary incentives to private physicians with no clinical research experience who persuade their vulnerable patients to sign up." They should be abolished, Wolfe said, as should finders' fees to physicians (typically in the range of \$1,000 to \$5,000 per patient).



Thomas Bodenheimer

Further cause for alarm over industry control of clinical studies was provided by Thomas Bodenheimer, clinical professor of family and community medicine at the UCSF School of Medicine, and a correspondent for the

NEJM. He presented data showing that published findings are nearly always favorable to the study drug when the study was funded by the drug maker and that study drugs are given more favorable write-ups when the author has financial ties to the sponsor.

He presented documented cases of faulty trial design (competing drugs given in ineffective doses or by inappropriate routes; study population substantially different from intended patient population), skewed data analysis (results reported only from those sites in a multicenter trial at which the study drug

did well), suppression of publication altogether in the face of unfavorable findings, "conclusions" in abstract or summary that are not supported by the data, and the use of hired "ghosts" to write reports under an investigator's name.

Remedies, he said, include separating sponsors from all aspects of study design, data analysis, and publishing. More funding of clinical investigators should come from NIH than from industry, he urged, and industry should funnel its budgeted clinical trial money through NIH and then walk away, leaving NIH to sponsor the trial.

### Some Policies and Practices

*From a professional society:* Savio Woo, president of the American Society of Gene Therapy, announced that his organization had adopted the policy that its members either refrain from participation in a study sponsored by a company in which they have a financial interest or, alternatively, give up that interest.

#### *At research institutions:*

■ At Boston Children's Hospital, said Susan Kornetsky, director of clinical research compliance, disclosure of financial interests accompanies research protocols submitted to the IRB, which decides whether and how much to inform research subjects (an IRB member with a conflict must leave the room during the final discussion and vote); all faculty must comply with Harvard policy, which places a ceiling on the amount of allowable financial gain; a trial may not be supervised or conducted by the inventor of the study product; recruitment fees and completion bonuses are prohibited; if the hospital has an equity interest, that must be disclosed in the informed consent document; and issues of budget, publishing rights, and data ownership must be agreed upon before protocol approval.

■ "There is no evidence that financial interests, which have become part of the research landscape, are inherently harmful," said Julie Gottlieb, executive director, Office of Policy Coordination, at Johns Hopkins University School of

Medicine in Baltimore, "but they require disclosure and review and their management is labor-intensive." Hopkins has a separate Conflict of Interest Committee, made up of senior faculty and administrators, that meets regularly and is advisory to the IRB. Hopkins policy requires reporting of all financial interests, however small and whatever the nature of the research—basic or clinical—and public disclosure in the patient consent form. Investigators with a financial interest may not be the principal investigator, obtain informed consent, or analyze data. Divestiture of financial interests and bottom-line rejection of the protocol are also possibilities.

### Summing Up

Greg Koski, the first director of the newly revamped HHS Office for Human Research Protections, summed up what he saw as areas of consensus:

■ Conflict of interest in clinical research is real and is a threat to clinical research.

■ Conflict of interest has intensified over the last two decades and has gotten "out of control" in the last five years.

■ Those conflicts of interest that cannot be eliminated completely must be "managed," and institutional review boards cannot do it alone. There need to be uniform guidelines throughout government—or, if compliance is lagging, then rules. ■



Greg Koski

### Have Your Say

Though the conference on "Human Subject Protection and Financial Conflict of Interest" unexpectedly drew nearly 800 registrants, several speakers observed that the meeting was short on clinical investigators and patients. Federal officials expressed the hope that some of that gap would be filled by written responses to six questions posed in the July 3 *Federal Register* to jumpstart the conference. For a conference overview, with links to the questions and other materials, visit

<<http://aspe.hhs.gov/sp/coi>>.

Responses may be sent to

<[coi@osaspe.dhhs.gov](mailto:coi@osaspe.dhhs.gov)>

or to Stuart Nightingale, Office of the Assistant Secretary for Planning and Evaluation, Hubert H. Humphrey Building, Room 447D, 200 Independence Ave., S.W., Washington, D.C. 20201.

The deadline is **September 30**. ■

### No Two Ways About It

Where do you draw the line on conflicts of interest? "Would it pass the '60 Minutes' test? If not, don't allow it." —Abbey Meyers, *National Organization for Rare Disorders*.

## A UNIQUE SUMMER PROGRAM: GENETICS AT THE NIH CLOISTERS

text and photos  
by Fran Pollner



**Partners:** Francine Nichols (left), the Georgetown University coordinator of the Summer Genetics Institute partnership forged by NIH's Annette Wysocki (right). The SGI, Wysocki says, is a fine example of the collaborations the NIH Graduate Partnership Program has been established to create (see "Catalytic Reactions," page 3).

Fourteen students were at the right place at the right time this summer—at the same time the completion of a draft sequence of nearly all of the human genome was announced, these students were navigating between lab and lecture room here, absorbing the message between those sequences, in the first season of the NINR Summer Genetics Institute (SGI). The program combines complementary lecture and lab sessions targeted to molecular genetics, together with case tutorials to place it all in a clinical context. Field trips (for instance, to the NCI microarray facility and the NHGRI sequencing facility) and a heavy dose of required and supplementary reading, round out the program—eight weeks of immersion in everything from cell biology and modes of inheritance to genetic counseling and family dynamics, including 150 hours of lab work. The institute received three applications for each position; more are anticipated next year, says Annette Wysocki, now of NIDCR and a driving force behind the program when she was NINR scientific director.

The 14 students selected for the pioneer program were all graduate students, faculty, or advanced practice nurses in academic medical settings. Two were nurse researchers, and six were completing their doctoral programs. Each applicant wrote a statement of interest, including how they planned to use the course in their research, practice, and educational activities.

The 12-credit graduate course is approved by Georgetown University (Washington, D.C.) and underwritten by NINR; the students receive IRTA stipends. Credit is not automatic; there are difficult midterm and final exams, and students must also craft a written research proposal in an ROI format. "You can get bits and pieces of this course elsewhere," says Wysocki, "but this is the only course with all of it."

The hope, she said, is that the course will serve as a model

and be re-created and incorporated into curricula across the country. NINR has already received inquiries about using materials developed for the program in other university settings. ■

### Into the Future

Ninety percent of the human genetic sequence in draft form is now sitting on the Internet for all to see—and maybe they'll help us figure out what it means," Francis Collins, head of the Human Genome Project, quipped to the soon-to-be first graduating class of the NINR Summer Genetics Institute.



Francis Collins (left) and Frank Castora answer additional questions after delivering the final lectures of the Summer Genetics Institute.

The precise gene variants contribute to the more common conditions—such as heart disease, diabetes, hypertension, and obesity—are not yet known, Collins said, "but that lies just ahead of us, and I worry: Are there providers out there? Will the information be used inappropriately? We need medical care givers and excellent research in this area, and I am delighted to see this cohort that is serious about genetics in nursing. Especially the way managed care has placed constraints on physicians, I think a lot of genetics will be practiced by nurses."

Collins described a collaboration between U.S. and Finnish investigators to track genes that confer a risk for type 2 diabetes—a paradigm of non-Mendelian genetics. Five thousand samples from more than 1,000 families, each with at least two affected siblings, now sit in Building 9 freezers, Collins said. "We scanned the genome and found four broad and blurry regions with, we think, contributing genes that we hope to zero in on in the next year or two." Similar scenarios can be expected for other conditions, he said. ■

Questions about the program should be addressed to: Summer Genetics Institute, Division of Intramural Research, NINR, NIH, 31 Center Drive, MSC 2178, Bethesda, MD 20892. ■

### On Their Way



Marcia Phillips (left), en route from Rush University, Chicago, to Seattle and lab partner Ann Cashion, of the University of Tennessee, Memphis.

Marcia Phillips has been a clinical nurse for 20 years—"everything from the neonatal unit to the emergency room to research"—and is now working on her doctoral dissertation on breast cancer genetics. This program, she said, of the Summer Genetics Institute, was "much more scientific at the molecular level [than any she'd experienced], and it gave me a much better understanding of the disease process. It opened up a new world" that will be passed along to her patients. There was also considerably more lab work than she'd ever been exposed to. "I didn't know what a pipette was, and now I've run Southern blots, done PCR, separated the DNA to determine which cells have mutations." Perhaps five nursing schools in the country have programs in genetics, she said, and none that she knows of compares with this one.

On the last day of classes, after hearing a two-hour lecture by Frank Castora of the Eastern Virginia Medical School in Norfolk (pictured above) on the mechanisms of mitochondrial genetics, Phillips and her classmates repaired to the lab downstairs, where they learned from Castora the hands-on mechanics of the "detection of mutation by single-strand conformational polymorphism." ■

## POSTCARDS FROM THE CUTTING EDGE OF SUMMER RESEARCH

text and photos  
by Celia Hooper

Dear Fran—Once again I was humbled by the sheer creative brilliance and energy that abounded at Poster Day—the annual display of research by NIH summer students. These kids are awesome!

It's Aug. 3, and I'm having a great time! Wish you were here!

Celia



### Postcard 1—Type B Insulin Resistance; Preceptor: Elif Arioglu, NIDDK

Melissa Bell, on the right, a 2nd-year medical student at the University of Oklahoma, talks about her diabetes research with LaShawn Drew, acting director of the NIH Academy. Bell said the thing that surprised her most about research here was all the rare diabetes-related syndromes she encountered. She wants to continue studying insulin resistance and says she would love to come back to NIH.



### Postcard 2—The Use of TCR Rearrangement Excision Circles (TRECs) as an Indicator of Immune Reconstitution in HIV-infected Patients Receiving HAART Therapy; Preceptor: Mark Dybul, NIDDK

Joshua Vásquez, an undergraduate in his junior year at the University of Wisconsin, was really excited about his research on a possible method for measuring reconstitution of the immune system in HIV patients. This guy has known since junior high that he wants to study HIV. . . . Plans to get an MD-Ph.D and will be back next summer. In this shot he's talking to Arlyn Garcia-Perez, assistant director of the Office of Intramural Research. Vásquez was in the Undergraduate Scholarship Program. He says two great things about NIH were the accessibility of scientists here—everyone was happy to talk to him—and the close proximity of basic and clinical research. In addition to his basic research with Mark Dybul, he was able to do some other clinically oriented work with Michael Polis.



### Postcard 3—Effect of Nitric Oxide Inhalation on Response to Vascular Injury; Preceptor: Richard O. Cannon III, NHLBI

Sharleen St-Surin, on the left, from Howard University College of Medicine in Washington, D.C., is going into her second year of medical school. St-Surin's work with Mark Gladwin of the CC and Betsy Nabel and others in NHLBI looked at NO gas as a treatment to reduce neointimal proliferation after vascular injury. This injury response may play a role in early restenosis after angioplasty or stent placement to open up atherosclerotic arteries. St-Surin found that NO after two weeks of inhalation was effectively taken up and transported via Fe<sup>2+</sup> in hemoglobin over the two-week experiment with a mouse model. As usual, one summer wasn't enough to get all the data, but others will continue the work . . . and St-Surin says she hopes to come back to NIH after she passes her boards. In this shot, St-Surin talks to Deborah Cohen of the Office of Education. Cohen played a lead role in organizing Poster Day.

## NIH Fellows Create Online Job Network

The NIH Fellows' Job/Alumni Network is a new online resource for NIH fellows nearing completion of their fellowships and looking for job leads. The Network will soon be accessible through the Fellows Committee web page (<http://ftp://helix.nih.gov/felcom/index.html>) and is seeking volunteers to provide info about potential employers.

If you are a postdoctoral fellow leaving NIH and would like to serve as a contact for other fellows seeking jobs in the future, or if you would like to advertise a temporary or permanent position, please send the following information to [szymkoy@nidcd.nih.gov](mailto:szymkoy@nidcd.nih.gov):

1) Type of job (such as research, administrative, teaching,

marketing/sales)

2) Relevant scientific areas (molecular biology, pharmacology)

3) Name, address, phone number, and e-mail address

4) Any other relevant information (in brief format)

The database is maintained by volunteers from the Web Subcommittee of the NIH Fellows Committee. Information supplied from volunteers will be posted for a period of up to two years. The database will grow only with input from NIH fellows, who are encouraged to submit their job information as they depart NIH—or at any time they have knowledge of an opening. ■

## PRAT: 35 YEARS OF TRAINING PHARMACOLOGY LEADERS

by Alisa Zapp Machalek, NIGMS  
and Michael Vatalaro, NIGMS

It allowed me to come to NIH and work in one of the best labs in pharmacology. It completely started my career," said Steve Paul, speaking about the Pharmacology Research Associate (PRAT) program sponsored by NIGMS. Paul, an M.D., became a PRAT postdoctoral fellow in 1976 to train in the NIMH laboratory of Nobel laureate Julius Axelrod. Paul rose to the rank of scientific director at NIMH and is now a group vice president at Eli Lilly and Company. "To this day," he said, "I continue to benefit from the work I did and mentorship I received as a PRAT fellow."

The PRAT program, a two-year postdoctoral fellowship in the pharmacological sciences, has trained leaders such as Paul for 35 years. It provides a cross-disciplinary environment for those who want to specialize in pharmacology or to apply their pharmacological training to other fields.

More than 90 percent of PRAT fellows have continued in research and research-related careers. Of these, 43 percent are in academia, 31 percent in government, and 25 percent in industry.

NIGMS, which does not have intramural research labs of its own, recruits and supports the fellows, who arrange to work in labs of their choice at NIH or FDA. Intramural senior scientists who serve as PRAT mentors add to their lab the expertise of a talented, carefully selected PRAT fellow.

The program's overall goal—to identify and train leaders in pharmacology—has not changed significantly over the decades, but the scientific scope of the program has become much broader, say PRAT co-directors Alison Cole and Pamela Marino, who are also extramural program directors in the NIGMS Division of Pharmacology, Physiology, and Biological Chemistry.

"We've had fellows come in with a pharmacology background who want to learn about neuroscience or bioinformatics, and we've had biomedical engineers who want to apply their expertise to pharmacological science," Cole said.

The PRAT program moves beyond the lab as well, with coordinated activities that provide networking opportunities and expose the fellows to the breadth of pharmacological research. There are monthly presentations of ongoing research by the second-year fellows and guest lectures on topics such as grantsmanship and career development.



Michael Vatalaro

PRAT co-directors Pamela Marino (left) and Alison Cole

"Since I am now in computational biology and I don't do wet bench experiments anymore, it's been great to attend PRAT seminars once a month to keep in touch with my former life," said Stephen Edwards, who is a first-year PRAT fellow at NCBI. "[These seminars] are one of the nicest things of the PRAT program and they benefit even people working in the labs because they're all working in different institutes, studying different systems, and using different techniques."

Edwards, who earned a Ph.D. in pharmacology from Vanderbilt University in Nashville, Tenn., said he also appreciates the career guidance that PRAT fellows receive from the program co-directors. "In graduate school and [typical] postdoc fellowships, they do a good job of training you what to do [in the lab], but they don't give you much information on career paths," he said.

"From the first meeting, the directors have given us a lot of good advice: You need to go to meetings, you need to give presentations, you need to be networking and meeting people. When the program is over, you haven't been holed up in the lab for two to four years without any outside contact."

Some fellows had such positive experiences that they became PRAT mentors, or preceptors, themselves. Michael Rogawski, now chief of the Neuronal Excitability Section of the Epilepsy Research Branch at NINDS, became a pre-

ceptor because he "wanted to give back to the PRAT program." He received his M.D.-Ph.D. from Yale and stretched his PRAT training out from 1981 and 1984 to fit in a neurology residency at Johns Hopkins. The first fellow who trained in his lab, N. Bradley Keele, is now an assistant professor of neuroscience at Baylor University in Houston. Rogawski has just taken on a new fellow, Melissa Banks (see "PRATs Past and Present," page 9).

Before applying to the PRAT program, each applicant must develop a scientific proposal with his or her chosen preceptor. The PRAT selection committee, which is made up of NIH and non-NIH scientists, evaluates prospective fellows and preceptors as a package during the competitive application process. Each year, the program accepts six or seven new trainees.

The PRAT program originated in the mid-1960s, when there was an increased awareness of how environmental toxins such as DDT affect human and animal populations. A committee commissioned by James A. Shannon, then the NIH director, recognized the importance of understanding how chemicals interact with

living systems—and that such interactions would daily grow more common. It recommended the formation of a training program to strengthen the country's pharmacological research capabilities. Over its 35-year history, the resulting PRAT program has trained 334 fellows with senior scientists at 14 different NIH



Michael Rogawski



## PRATs Past and Present

text and photos by Michael Vatalaro

Many PRAT fellows have gone on to highly successful careers in academia, industry, and government, but perhaps none so visibly as Alfred G. Gilman, co-recipient of the 1994 Nobel Prize in physiology or medicine. Gilman and the late Martin Rodbell, who did his prize-winning research while at what was then called the National Institute of Arthritis and Metabolic Diseases, won the prize "for their discovery of G-proteins and the role of these proteins in signal transduction in cells." In his autobiography, Gilman describes his time in the program between 1969 and 1971 as "enormously broadening."

Given its reputation and the unparalleled resources available at NIH, the PRAT program recruits a wide variety of postdoctoral candidates from around the country. The newest PRAT fellow on campus, Melissa Banks, came from Indiana University, Bloomington, where she earned a dual Ph.D. from the Department of Psychology and the Program in Neural Science. She is conducting research on epilepsy in a rat model. Her lifelong interest in epilepsy originated in childhood, with her experiencing a seizure herself and undergoing five years of treatment before the condition was vanquished.

Banks said she joined the PRAT program to gain more experience in phar-



Melissa Banks

macological research techniques, including in vivo work and electrophysiology and other methods. She expects that the program will enable her to work more independently than her graduate studies allowed and that she will be involved in epilepsy research after completing her fellowship. Banks works in the NINDS lab of former PRAT fellow Michael Rogawski.

Second-year PRAT fellow Catherine Booth studies with Ira Pastan in the Laboratory of Molecular Biology at NCI. She focuses on P-glycoprotein transporter molecules, trying to determine the structure and function of the proteins' nucleotide binding domains. Her broad goal is to understand how ATP interacts with the transporter and how the transporter harnesses energy from ATP hydrolysis. Booth earned her Ph.D. at the University of North Carolina, Chapel Hill, and worked for a pharmaceutical company before coming to NIH.

Booth says the PRAT program has given her the opportunity to meet and interact with her peers and has also provided many guest speakers to discuss topics relating to careers outside of NIH. Looking back over her time as a fellow, which is drawing to a close, she said the experience was "overwhelming, the first few months. The level of science is above all others.

There are a ton of talented people." Booth said she hopes to continue doing applied

research, primarily in the area of targeted drug delivery.

Luci Roberts, who has a Ph.D. in zoology, specializes in behavioral studies, specifically the neuroendocrinology of social behavior. Working in the Laboratory of Comparative Ethology at NICHD, Roberts examines the role of dopamine, serotonin, and related hormones in the social bonding and parental behavior of common marmosets, small New World primates that live in nuclear family units.

Roberts' research strays from the norm in behavioral pharmacology. She studies the hormones that make marmoset families happy, cohesive units. More commonly, researchers look at aggression and maternal separation and other negative consequences of hormone imbalance or deficiency. Since completing the PRAT program in February, Roberts has secured a K22 Career Transition Award, which will allow her to continue her research at NICHD for the next two years while she looks for a tenure-track position locally.

"PRAT and the K22 give me an edge," she said. ■



Catherine Booth

institutes and one FDA branch.

Cole and Marino hope to promote the program further at NIH and nationally and to bring intramural scientists from additional institutes onto the program's advisory committee and into the ranks of preceptors.

The program's success shines through its graduates, including one Nobel Prize winner—Alfred Gilman (see "PRATs Past and Present"). "Many PRATs are now leaders in the field [of pharmacology]," said co-director Marino. "They're starting their own companies; developing their own research labs in industry, academia, and government; and doing interdisciplinary research." ■

## Next PRAT Cycle on the Horizon

The deadline for applications to the NIGMS Pharmacology Research Associate (PRAT) Program is **January 3, 2001**, for positions starting in October 2001. The PRAT Program supports two years of training in laboratories at NIH or FDA for postdoctoral candidates in the pharmacological sciences and related research areas. These may include but are not limited to molecular pharmacology, signal transduction mechanisms, drug metabolism, immunopharmacology, chemistry and drug design, structural biology, endocrinology, bioinformatics, and neuroscience. PRAT Fellows receive competitive salaries as well as supply and travel funds to support research in their preceptors' laboratories. Candidates apply in conjunction with an identified preceptor, who may be any tenured or tenure-track scientist at NIH or FDA. For more information or application materials, contact the PRAT Program Assistant at 301-594-3583 or <[PRAT@nigms.nih.gov](mailto:PRAT@nigms.nih.gov)>.

Another PRAT program, launched two years ago and open to individuals with M.D. degrees, is designed to create a cadre of scientists in the clinical development, evaluation, and therapeutic use of small molecule- and biotechnology-based pharmacotherapy. For more information on the **Clinical Pharmacology PRAT program**, contact Art Atkinson at 301-435-8791 or visit <<http://www.cc.nih.gov/OD/clinprat/>>. ■

## PREVENTING AND RESOLVING PERSONAL AND WORKING CONFLICTS: THE OMBUDSMAN IS IN AT NIH

by Cynthia Delgado

In 1997, NIH launched a pilot project to establish the Center for Cooperative Resolution (CCR) headed by the first ombudsman, David Lee Robinson (former chief of the Visual Behavior Section, NEI). The center was to serve as a confidential and neutral site for early-intervention conflict resolution for all NIH employees (see *The NIH Catalyst*, January-February 1997, page 4; <<http://catalyst.cit.nih.gov/catalyst/back/97.01/ethics.html>>).

The pilot project served five institutes for 18 months before it officially opened to all of NIH in 1999 with a new ombudsman, Howard Gadlin, at the helm, aided by Robinson, who worked with Gadlin during the transitional first year.

Both the pilot project and the first full-service year were quite successful, says Gadlin. Questionnaires and feedback from the people who used the office during the pilot period were "quite positive." They deemed the office "very effective," he says. And in 1999, the CCR handled more than 300 cases involving close to 800 people and set into motion new mechanisms to resolve conflicts of a systemic nature in a more fair manner (such as peer review panels) and to prevent common sources of conflict from arising in the first place (such as early-stage partnering agreements regarding such issues as work expectations and authoring—a "prenuptial" for scientist collaborators and mentors and mentees, according to the CCR Annual Report for 1999).

"The center is really just this office," says Gadlin of his home in Room 1B39 in Building 31. It's called a "center," he says, because "we do things [in addition to] one-on-one conflict resolution" (such as facilitating meetings and conducting employee training and seminar series for management) and we are also the focal point for conflict management at NIH."

Previously a tenured professor at the University of Massachusetts with a background in experimental psychology and a penchant for visual perception, Gadlin says he "got into [the role of] ombudsman by accident." What he viewed as a "two-year break from my regular job"—at UCLA—turned into his regular job. "I got totally intrigued with it, so I kept being renewed." He served as UCLA's ombudsman for seven years until being lured away by NIH.

Gadlin is assisted here by Doris Campos-Infantino (deputy ombudsman) and Kathleen Moore (associate ombudsman), with whom he balances the workload. (Two more people are slated to be hired

to replace others who are leaving.) The CCR staff also sets aside time for a monthly journal club to discuss the latest approaches to conflict resolution. The center collaborates with other service organizations on campus and with external groups (such as the Institute for Conflict Analysis and Resolution at George Mason University in Fairfax, Va.).

"The basic idea of an ombudsman's office, Gadlin says, "is to have a place where people can come to address grievances and concerns without, or before, going into any formal procedures. The office should be confidential, neutral, independent, not part of management, [and] without decision-making ability, and serve as an intermediary between disputing parties," Gadlin says. There are many ways, he observes, that one can be unhappy in the workplace that do not involve a violation of rules or rights. Indeed, there are some concerns for which "there are no policies or procedures, nor would you even want or expect to have policies or procedures."

Among the advantages of using the CCR as an alternative route to formal dispute resolution are the degree of personalized attention each case receives and, by virtue of less red tape, the relative speed with which conflicts are likely to be resolved. "We have the latitude to develop a mode of intervention that's appropriate to the situation. We don't have a fixed procedure." The process is also less adversarial. "If you file a formal grievance against your boss," Gadlin comments, "it's automatically framed in an adversarial way. You're saying, 'This happened...She's at fault.'"

When an individual approaches the ombudsman, Gadlin and his associates hear his or her complaint and desired outcome and "get their sense of the situation." Sometimes a person "merely wants some advice or help in reviewing a letter they have written to ensure it conveys what they want it to convey." Some of the techniques used to help are *facilitated discussion* (between conflicting parties), *mediation* (using a third-party diplomat), or a *generic approach* (correcting a system's problem while the particular complainant remains anonymous).

Because confidentiality is paramount, there are no written records related to individual cases, but the office does maintain statistical records of complaints



Cynthia delgado

**The Ombuds Circle:** (left to right) Howard Gadlin, Kathleen Moore, and Doris Campos-Infantino

handled, processes used, and types of resolutions achieved. According to the CRC annual report for 1999, nearly 75 percent of the 328 cases brought that year involved issues related to work environment, management, and personnel matters. Six percent of cases related to research. More than 40 percent were closed within two weeks and nearly all within six months. Sixty-six percent were fully resolved, including several complex, multiparty scientific disputes.

Gadlin notes that he has "gotten much more interested in doing early intervention and conflict prevention than ever before," an interest reflected in the emphasis placed in the annual report on "partnership agreements" among scientist collaborators and mentors and postdocs. "A partnership agreement is essentially a prenuptial agreement for scientists," the report observes.

"In our experience, many of the conflicts that arise between scientists could have been avoided had the parties to the conflict begun their collaboration with an explicit agreement about their expectations of each other and about how they would handle the major transactions of the collaboration." The office is developing formal partnering agreements it expects to finalize this year and hopes their use will become standard practice within five years.

Partnering agreements, Gadlin says, are "not just a way of preventing conflict but also of fostering the sorts of working relationships that enable people to do better science." The office also hopes to find ways to address racial tensions at NIH and, all in all, "change the culture of NIH in ways that increase its ability to fulfill its mission."

The CRC may be reached at (301) 594-7231; for more information, visit <<http://www4.od.nih.gov/ccr/>>.

**VRC MATERIALIZES**  
continued from page 1

the cornerstone of the Dale and Betty Bumpers Vaccine Research Center, was dedicated in a ceremony attended by the president (see *The NIH Catalyst*, July-August 1999, page 14).

And a little more than one year later, although the first floor—housing the conference center, cybercafe, and director's quarters—was still awash with construction workers, most of the four floors of labs and offices above was in working order.

The second week in September, VRC Director Gary Nabel moved into the building, taking up temporary administrative quarters on an upper floor and taking root in his new lab, where he and his team—which was moved from the University of Michigan, Ann Arbor, where Nabel had been director of the Center for Gene Therapy—resumed their research (see photo below). John Mascola and Mario Roederer—two new recruits—also moved into their respective labs and offices. In all, there were 20 researchers on site out of an anticipated 100 or so at full occupancy.

Among people already named to key VRC positions are:

- Gordon Douglas, director of strategic planning
- Barney Graham, director for human clinical studies
- Norman Letvin, director of the Non-Human Primate Research Program

- John Mascola, VRC deputy director

- Mario Roederer, director of the Flow Cytometry Core Lab

Following are brief descriptions of these individuals, culled from more detailed biographical profiles that appeared in *The NIH Record*, July 25, August 8, and August 22.

Gordon Douglas, director of strategic planning, held academic and clinical positions in medicine and infectious diseases before joining the corporate world as an officer in Merck & Co. and president of Merck Vaccines. A primary focus for Douglas will be forging collaborations between the VRC,



Fran Pollner

**About half of the Nabel lab:** (left to right) Ling Xu, Yongnian Sun, Zhi-Yong Yang, Yue Huang, Masa Kurooka, Bimal Chakrabarti, and lab manager Kwanyee Leung. Some of the scientists have been in temporary quarters in Building 10 for about a year and are in various stages of transition to Building 40; others, like Nabel's lab manager, who closed down the Michigan lab August 31, came directly to the VRC and had been here only about two weeks when this photo was taken. The team has been working on enhancing the immunogenicity of selected HIV antigens, focusing especially on two targets—gag pol and an envelope protein. Preliminary testing of mutants of these proteins has yielded promising results in mouse models. This research is proceeding in tandem with work on vector constructs.

academia, and the pharmaceutical and biotechnology industries.

Barney Graham, director for human clinical studies and a tenured investigator, was a professor of medicine and associate professor of microbiology and immunology at Vanderbilt University School of Medicine in Nashville, Tenn. He helped establish NIAID's AIDS Vaccine Evaluation Group, the network of centers that tests candidate AIDS vaccines in humans, and for the past 13 years headed Vanderbilt's AVEG unit. Graham will shape the VRC's clinical trials program. (For details of Graham's research, see *The NIH Catalyst*, July-August 2000, "Recently Tenured," p.11).

Norman Letvin, director of the Non-Human Primate Research Program, was immunology chairman at the New England Regional Primate Research Center of the Dana-Farber Cancer Institute in Boston before becoming chief of viral pathogenesis at Boston's Beth Israel Deaconess Medical Center, a position he will maintain in conjunction with his VRC responsibilities. Letvin will choreograph the movement of vaccine candidates from VRC labs into nonhuman primate models.

John Mascola, VRC deputy director, headed HIV prevention research and had a lead position in HIV vaccine development at the Walter Reed Army Institute of Research in Washington, D.C. In addition to overall VRC planning, Mascola will oversee the basic and applied research activities conducted at the VRC's biosafety level 3 facility.

Mario Roederer, director of the Flow Cytometry Core Lab, did postdoctoral research in immunology at Stanford (Calif.) University before becoming an adjunct associate professor of stomatology at UCSF. At the VRC, Roederer will also continue his basic research on T-cell subsets, antigen-specific immunity, and mucosal immunity. ■



Fran Pollner

**A lab of one's own:** The office space is adjacent to the lab space and lit by floor-to-ceiling windows. Shown here is one of the several "bays" devoted to VRC Director Gary Nabel's lab. There are 10 such bays on each typical VRC lab floor—and no doors. Four lab spaces and four office spaces are contained within each bay, but the design allows for flexible rearrangements based on each lab's needs.



Fran Pollner

**Flow chart:** Mario Roederer, who spearheaded the development of 11-color flow cytometry at Stanford and brought it with him to the VRC, will run the VRC's Flow Cytometry Lab (above; housed on the top floor, along with the BSL3 facility and several other labs). Roederer has been examining the activities of naive CD4+ T cells in AIDS progression.

## RECENTLY TENURED

**Steven Holland** received his M.D. degree in 1983 from the Johns Hopkins University School of Medicine in Baltimore, where he was chief resident in internal medicine and a fellow in infectious disease before joining the Laboratory of Molecular Microbiology, NIAID, in 1989. In 1991, he joined the Laboratory of Host Defenses, NIAID, where he is now a senior clinical investigator.

My interests are broadly in the area of immunodeficiencies, especially as they affect phagocytes. I joined the laboratory as part of the research effort in chronic granulomatous disease (CGD), a pediatric immunodeficiency in which neutrophils fail to make superoxide and are therefore unable to produce hydrogen peroxide and bleach. The condition is characterized

by severe recurrent bacterial and fungal infections, as well as severe granulomatous reactions that can obstruct internal organs and impair wound healing.

Early on, my colleagues and I used homologous recombination to create a mouse model of the most common autosomal recessive form of CGD. This model has furthered our understanding of granulomatous reactions. We have used it in gene therapy studies and are currently exploring some of the less anticipated ramifications of CGD. For instance, superoxide generated by the NADPH oxidase appears to be very important in the development of experimental allergic encephalomyelitis (EAE), ethanol-induced liver damage, and antigen-induced joint damage. We are using these animals, in conjunction with collaborators in the Laboratory Host Defenses and around the world to better dissect the critical roles that superoxide plays in signal transduction and immune modulation, as well as in host defense.

In caring for patients with CGD, I encountered a family with an apparent genetic susceptibility to mycobacterial infection. We treated these patients with interferon gamma, a critical downstream gene induced by IL-12, and had dramatic clinical results. Subsequently, Dave Frucht in the lab showed that this particular family has a problem affecting IL-12 production. This led us to develop a very successful clinical protocol using interferon gamma to treat patients with severe, refractory, nontuberculous my-



Fran Pollner

Steven Holland

cobacterial infections.

In the course of our studies we identified several patients with genetic mycobacterial susceptibility who did not respond to interferon gamma therapy. Further study revealed associated mutations in interferon gamma receptor 1. With Susan Dorman in the lab, we then identified the first patients with mutations in interferon gamma receptor 2.

This in turn has led us to collaborations with groups in Europe to identify the most common mutation in interferon gamma receptor 1, an autosomal dominant mutation at base 818.

We began these studies in mycobacterial disease in an effort to provide treatment for patients who were critically ill and had no further therapeutic options. As a result,

we have been successful at identifying important pathways for future therapeutic exploration, as well as pathways that, when disrupted, lead to profound susceptibility to mycobacterial, fungal, and certain viral infections. It does not appear that general susceptibility to *Mycobacterium tuberculosis* is caused by mutations or polymorphisms in the same genes that cause susceptibility to nontuberculous infections. However, we have active protocols investigating the possibility that therapy using the interferon gamma and IL-12 pathways will be successful, especially in cases of severe multidrug resistant tuberculosis.

**Robert Kreitman** received his M.D. in 1985 from Ohio State University in Columbus and completed clinical training in internal medicine at Duke University Medical Center, Durham, N.C., in 1988. During and after training in medical oncology at NIH, he worked in the Laboratory of Molecular Biology, NCI. He is now chief of the Clinical Immunotherapy Section in that lab, where he oversees translational and basic studies. He also serves as principal investigator for clinical trials conducted in the Clinical Center by the Medicine Branch of the NCI Division of Clinical Sciences.

I have been involved in the preclinical and clinical development of recombinant immunotoxins for the treatment

of cancer and autoimmune disease. These agents contain an Fv domain, which binds to tumor-selective antigens, and a bacterial toxin (*Pseudomonas* exotoxin), which can kill a cell when only one or a few molecules reach the target cell's cytoplasm. Recombinant immunotoxins are produced in large scale by plasmids in *Escherichia coli*. The resulting inclusion body protein is harvested and denatured, refolded in a redox buffer, and finally purified via ion-exchange and sizing chromatography.

In 1989, under the direction of Ira Pastan, I began testing the first recombinant immunotoxin made, anti-Tac(Fv)-PE40, which was engineered by Vijay Chaudhary. We tested this agent in freshly isolated peripheral blood malignant cells from patients with leukemia. The target cells included both B- and T-cell leukemias, Hodgkin's disease (HD), and activated T-cells that mediate autoimmune disorders such as graft vs. host disease (GVHD). We chose freshly isolated cells because we realized that cancer cell lines are often unrealistic models for human leukemia—they display higher numbers of receptors and are more metabolically active and homogenous than malignant cells

in patients. The binding portion of the agent is derived from Anti-Tac, the antibody to the interleukin-2 (IL-2) receptor alpha fragment (CD25) developed by Thomas Waldmann at NCI. We hypothesized that if fresh leukemic cells from patients could be killed by recombinant immunotoxin

ex vivo, and comparable concentrations of immunotoxin could be reached in the blood of patients, then patients would also respond. We found anti-Tac(Fv)-PE40 and a slightly shorter derivative, anti-Tac(Fv)-PE38, nicknamed LMB-2, were, indeed, cytotoxic ex vivo against cells from a variety of leukemias, including adult T-cell leukemia (ATL), chronic lymphocytic leukemia (CLL), and hairy cell leukemia (HCL).

We next developed an animal model to evaluate the agent's efficacy and safety in vivo and began a phase I trial of LMB-2 in 1996. I was principal investigator of the clinical protocol, in collaboration with co-investigators Wyndham Wilson of NCI's Medicine Branch, Thomas Waldman of NCI's Me-



Margaret Coulombe

Robert Kreitman

tabolism Branch, and Ira Pastan of LMB. We found that LMB-2 was effective at the maximum tolerated dose, with major responses in ATL, CLL, cutaneous T-cell lymphoma, HD, and especially HCL, where one complete remission and three partial responses were observed in four patients who were resistant to chemotherapy.

Access to patient samples yielded new observations and conclusions about how immunotoxins poison cells and traffic to the cytoplasm.

These studies also led to a better understanding of mechanisms of toxicity of immunotoxins in normal cells. We now plan to continue testing LMB-2 in patients with CD25+ malignancies and also in transplant patients, to prevent or treat GVHD.

In collaboration with Pastan and David FitzGerald of the LMB, we engineered the recombinant anti-CD22 immunotoxin, BL22, which improved targeting of B-cell malignancies. In preclinical studies, BL22 killed fresh human malignant B-cells *ex vivo* and also killed CD22+ tumors in mice. Since February 1999, I have treated 31 CD22+ CLL, HCL, or lymphoma patients with a total of 99 cycles of BL22. Both CLL and HCL patients have benefited clinically. BL22 is an excellent agent for either chemotherapy-refractory HCL or the poor-prognosis HCL variant, and many complete remissions have already been observed.

Several other agents produced in my lab are now being tested in clinical trials outside NIH. One of these is a circular IL-4 toxin, a single-chain recombinant toxin with the ligand-toxin junction at a location distinct from either the amino or carboxyl terminus of the ligand (see figure). This new ligand-toxin junction minimizes interference of the toxin with binding to the IL-4 receptor (IL-4R). Further preclinical and clinical development of this agent proceeded in collaboration with Pastan, Raj Puri of the FDA, and Robert Rand of the John Wayne Cancer Institute, Neurosurgery Department, in Los Angeles. The agent is currently being tested in patients with recurrent high-grade brain tumors,

which are usually IL-4R+. The agent has already induced complete remissions and several other positive responses.

Finally, a fusion of granulocyte-macrophage colony stimulating factor with truncated diphtheria toxin (DTGM) was made in my lab and, in collaboration with Arthur Frankel of Wake Forest University in Winston-Salem, N.C., is now being tested in patients with recurrent acute myelogenous leukemia. Although test doses are currently very low, we have documented major positive responses.

Our goal is to continue developing recombinant immunotoxins as a therapeutic modality distinct from chemotherapy, surgery, and radiotherapy. These agents may be useful in patients failed by traditional treatments, but may also prove effective in synergistic combinations with chemotherapy, be-

cause their toxicities are quite different. My lab is now exploring new immunotoxins to target other antigens important in other types of hematologic malignancies.

Beyond these malignancies, I have recently begun trials of recombinant immunotoxins for solid tumors. Treating solid tumors with this approach is more challenging than hematologic malignancies, as the agents are more immunogenic in these patients and less able to penetrate solid tumors; nevertheless, we hope to be able to overcome these hurdles.

**Paul Randazzo** earned his MD/PhD from Brown University in Providence, R.I. He received residency training in anatomic pathology and did postdoctoral work at the University of Pennsylvania in Philadelphia before joining NCI in 1990. He is a senior investigator in the Laboratory of Cellular Oncology.

I am interested in the regulation of the Arf family of monomeric GTP-binding proteins. The Arfs were first identified as cofactors for cholera-toxin-catalyzed ADP-ribosylation of the heterotrimeric G-protein, Gs. Subsequent studies have identified physiologic roles for Arf in

membrane traffic and the actin cytoskeleton. Six mammalian Arfs have been identified, with multiple Arfs occurring within single cells.

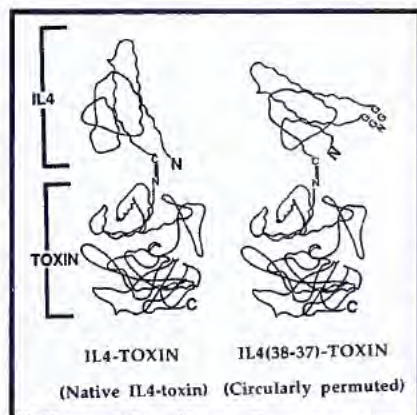
Because a single Arf gene product can affect multiple membrane trafficking events, each Arf must be independently regulated. In addition, the Arfs affect constitutive as well as acutely regulated processes. The function of the Arfs, like other GTP-binding proteins, depends on the controlled binding and hydrolysis of GTP. Guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs) control the cycle of GTP binding and hydrolysis and, as we and others are finding, contribute to Arf-specific and site-specific regulation. Some GEFs and GAPs are targets of signal transduction through cell surface receptors. Examination of the GEFs and GAPs has also been useful for understanding the function of Arf itself.

Recognizing that the GAPs might be site-specific regulators of specific Arfs and targets of signal transduction, we set out to purify a phosphoinositide-dependent Arf GAP. Through these efforts, we identified ASAP1 (Arf GAP with SH3,

ANK repeat, and PH domains), a multidomain protein that contains phosphatidylinositol 4,5-bisphosphate-dependent GAP activity and binds the tyrosine kinase, Src. Subsequent studies found that ASAP1 is associated with and regulates focal adhesions. The Arf GAP activity is necessary but not sufficient to

affect the focal adhesions, raising the possibility that ASAP1 is an Arf effector. Recent studies from other labs have found that ASAP1 can bind to paxillin and a GEF for Rho family proteins, PIX. Therefore, ASAP1 could be a key molecule in coordinating the activity of two families of GTP-binding proteins, the Arfs and Rhos, and, consequently, membrane traffic and actin cytoskeleton reorganization. One focus of the lab is to understand the molecular basis for ASAP1's activity, including ASAP1's role as a target for signal transduction through phosphoinositides and tyrosine kinases.

Based on sequence homology, a number of Arf GAPs related to ASAP1 have been identified, including PAP, ARAP1/2, ACAP1/2, and AGAP1/2. Like ASAP1, these proteins contain multiple domains that potentially interact with a number



Frank Palmer

Paul Randazzo

## PEOPLE

## RECENTLY TENURED

of signaling molecules. AGAPs contain a ras-like domain. They also have five PH domains and a Rho GAP domain. Preliminary studies indicate that all of these proteins affect cellular events that require coordination of membrane traffic and the actin cytoskeleton. By examining representative members of each family, we will test whether the Arf GAPs do provide Arf-specific and site-specific regulation and learn about the diversity of the signals targeting the Arf proteins. We also expect the studies will provide insights into the mechanisms regulating complex cellular events, like movement and phagocytosis, which involve membrane and actin remodeling

**Thomas Ried** received his M.D. from the University of Heidelberg, Germany, in 1989 and did postdoctoral work in David Ward's and Thomas Cremer's laboratories (Yale University, New Haven, Conn., and Heidelberg, respectively). He joined NHGRI in 1994 and NCI in 1998. He is a senior investigator in the Genetics Department, Medicine Branch, DCS/NCI.

Comparative genomic hybridization (CGH) of more than 500 carcinomas in our laboratory has revealed that genomic imbalances, as a result of unbalanced chromosomal translocations or chromosomal gains and losses, are the premier cytogenetic event in solid tumors of epithelial origin.

Our CGH analyses have focused on colorectal adenomas, carcinomas, and metastases and ovarian carcinomas. We compare the cytogenetic profiles of these tissues with gene expression analyses to understand the functional consequences of chromosomal aneuploidy.

Our recent comparison of 25 solid-tumor cell lines using spectral karyotyping and CGH has provided compelling evidence that the vast majority of epithelial cancers are associated with aberrations in either the number or structure of chromosomes, resulting in genomic imbalances. The comparison of diploid, mismatch repair-deficient colorectal carcinomas with aneuploid carcinomas indicates that numerical chromosomal aberrations are 60 times as prevalent in the aneuploid tumors. Abnormalities of the centrosome are correlated with chromosomal aneuploidy both in human cancer cell lines and in animal cells deficient for cell-cycle regulator genes such as *p53* and *BRCA1*. All

these results taken together support the notion that chromosomal aneuploidy is a major theme in epithelial cancers.

In order to elucidate mechanisms leading to aneuploidy, to establish the functional relevance of chromosomal aneuploidy, and to identify whether aneuploidy is a cause or a consequence of genetic changes in solid tumors, we have focused on the following projects:

- Structural and functional analysis of abnormal centrosomes and their relationship to chromosome segregation fidelity

- Live cell imaging of clonally derived cells after transfection with  $\alpha$ -tubulin green fluorescent protein (GFP) and CenPB-GFP vectors

- Sequential inhibition of *p53* and *Rb* function with E6 and E7 genes from human papilloma virus 16 and subsequent analyses of chromosomal instability

- Microcell-mediated chromosome transfer and in vitro induction of chromosomal aneuploidy in cells derived from normal colorectal epithelium and adenomas, followed by cytogenetic analysis and assays for cellular immortalization and transformation

- Comparison of cells carrying chromosomal aneuploidies with their wild-type parental cells using cDNA microarrays and 2-D gel protein electrophoresis

Efforts to define the sequence of genetic aberrations during human carcinogenesis increasingly depend on animal models, as does the understanding of the biology of tumor progression and the development of test systems for novel therapeutics. Murine models of human carcinogenesis are widely used to delineate genetic mechanisms that determine tumor initiation and progression, and improved methods for genetic manipulation open new avenues to study biological pathways of tumorigenesis. For this reason, we have worked hard to develop molecular cytogenetic tools to analyze chromosomal aberrations in mouse models of human cancer. Karyotype analyses of chemically induced plasmacytomas in mice, in lymphomas from *ATM*- or *Ku80*-deficient animals, and in mice transgenic for *c-myc* have provided evidence for the con-



Fran Poliner

Thomas Ried

servation of mechanisms leading to chromosomal aberrations across species boundaries. We have also been able to validate mouse models of human cancers by comparing the pattern of cytogenetic abnormalities with orthologous maps of human chromosomes.

Finally, we are interested in applying the knowledge

of specific chromosomal aberrations to the diagnosis of cancer in cytological preparations. For instance, more than 90 percent of cervical carcinomas carry extra copies of chromosome 3, and virtually all diploid breast cancers show a gain of chromosome 1q. Also, gains of chromosome 3q precede copy number increases of chromosomes 5p and 1 and loss of chromosome 2 during the genesis of cervical carcinomas. It is therefore helpful to use these recurring and specific chromosomal aberrations to complement and enhance the cytomorphological diagnosis of human cancers and their precursor lesions. This can be achieved using cytogenetics with fluorescently tagged DNA probes that recognize specific chromosomal target regions directly in interphase cells. We have focused on three applications:

- Identification of the progressive potential of cervical intraepithelial neoplasia based on the detection of extra copies of chromosomes 3 and 5 in thin-prep PAP smears

- Visualization of specific chromosomal aneuploidies in cytokeratin-positive epithelial cells isolated from the peripheral blood of breast cancer patients

- Diagnosis and prognostication of suspicious breast lesions following the detection of chromosomal aneuploidies in fine needle aspirates ■

### A New Flag



Celia Hooper

Richard Wyatt (center), OIR executive director, was sworn in as assistant surgeon general in August by Deputy Surgeon General Kenneth Moritsugu, as his wife, Linda, lends a steadying hand.

## WFLC Programs

**Phases of Life.** The third annual "Faces and Phases of Life" weekly seminar series, sponsored by the NIH Work and Family Life Center (WFLC), in conjunction with the Employee Assistance Program, kicks off in September. The October schedule follows.

"Helping Your Child Apply to College," Tuesday, Sept. 26, 12:00-1:30, Bldg. 31, Rm. 6C10

"The Basics of Collaborative Problem-Solving," Tuesday, Oct. 3, 12:00-1:30, Bldg. 31, Rm. 6C6

"The Nuts and Bolts of Choosing Child Care," Wednesday, Oct. 11, 12:00-1:30, Bldg. 31, Rm. 6C6

"Life Coping Skills (and Avoiding the Pitfalls)," Tuesday, Oct. 17, 12:30-2:00, Bldg. 31, Rm. 6C10

"Creating an Individual Development Plan," Wednesday, Oct. 25, 12:00-2:00, Bldg 31, Rm. 6C10

Seminars are free and videocast at <http://videocast.nih.gov>. To register for a seminar, call 301-435-1619 or e-mail at [wflc@od.nih.gov](mailto:wflc@od.nih.gov). A full schedule is available at the WFLC web site:

<http://wflc.od.nih.gov>.

**Lactation Program.** The two-year-old pilot NIH Lactation Program has been so successful that come October it becomes a permanent WFLC program.

Thus far, the WFLC lactation consultant has assisted more than 300 women. Services include:

- Prenatal breastfeeding education classes taught at various locations on campus

- Telephone support while on maternity leave

- Return to work consultation

On-site lactation rooms, equipped with breast pumps, are in buildings 10, 31, 45, 49, Rockledge II, the Neuroscience Research Center at 6001 Executive Blvd, and a temporary location in the EPN-EPS complex.

Additional information and an online registration form are available at <http://lactation.od.nih.gov> and from the lactation program's administrator Jane Balkam at (301) 435-7850 or [balkamj@od.nih.gov](mailto:balkamj@od.nih.gov).

WFLC is in Building 31, Room B3C15. For more information about services and programs, call 301-435-1619 or visit <http://wflc.od.nih.gov>.

**Resource Fair.** A resource fair, "Real People, Real Choices: Quality of Work Life at NIH" will be held Thursday, **October 5, from 10:00 am to 3:00 pm.** at the Building 10 Visitor Information Center (lower level exhibit area).

Sponsored by the NIH Quality of Work Life Committee, the fair will showcase the services of 26 NIH offices and organizations created to help enhance the quality of life of NIH employees. Included are:

- NIH's family-friendly workplace policies

- On-campus childcare centers
- Childcare and elder-care resource and referral services

- Programs that make the campus safe

- R&W's new concierge service
- Alternative dispute resolution

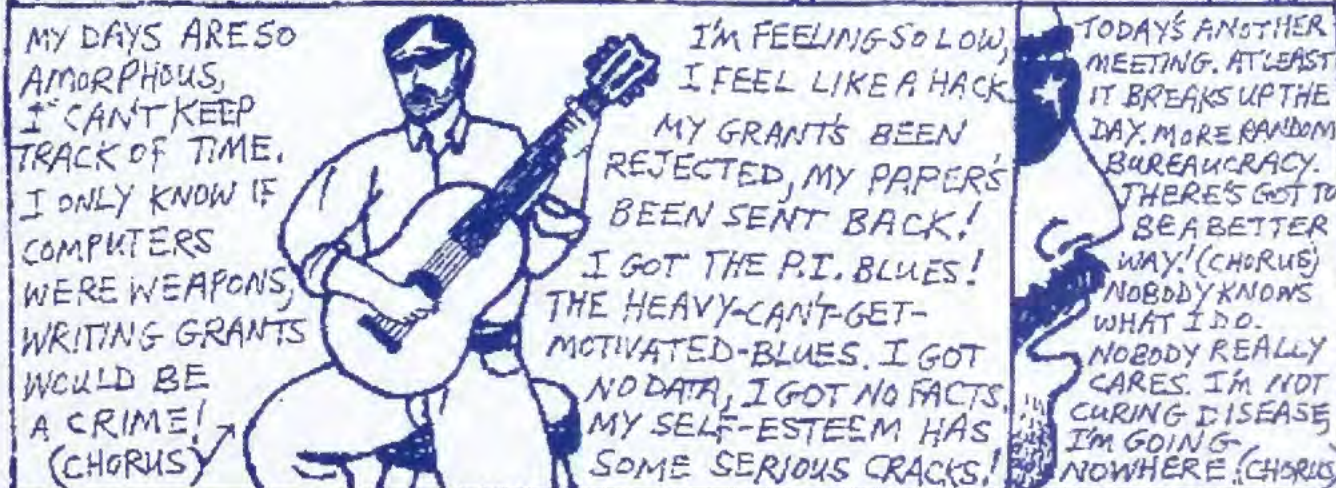
Keynoter Linda Breen Pierce, author of *Choosing Simplicity: Real People Finding Peace & Fulfillment in a Complex World*, will speak at noon in Lipsett Auditorium. For more information, call 301-435-1619 or visit the WFLC web site at

<http://wflc.od.nih.gov>.

## New Interest Group Forming Around End-of-Life Issues

The organizational meeting for the End-Of-Life Special Interest Group will be on Wednesday October 4 at 4PM in Bldg 31, Room 6C7. For more information, contact Ann Knebel at 301-402-6796 or [knebela@mail.nih.gov](mailto:knebela@mail.nih.gov).

## National Institutes of the P.I. Blues, part II



Alex Dent was an NCI postdoc from 1992 to mid-1998 and Catalyst cartoonist since the publication began in 1993. Notorious for his trenchant humor about the life of NIH postdocs, his cartoons are now inspired by being an assistant professor and PI at Indiana University School of Medicine. The above cartoon dramatizes some of the difficulties of starting out as a PI. The author would like to emphasize that the pessimistic tone portrayed in the cartoon is to be taken tongue-in-cheek, and importantly, the author does not wish to dissuade anyone from entering the scientific profession.

## CALL FOR CATALYTIC REACTIONS

In this issue, we are asking for your reactions in four areas: financial conflict of interest in clinical research, volunteering your time, the ombudsman's role at NIH, and retirement.

Send your responses on these topics or your comments on other intramural research concerns to us via e-mail:

<catalyst@nih.gov>;  
fax:402-4303; or mail:  
Building 2, Room 2W23.

### In Future Issues...

- 10 and Counting:  
ORWH & ORMH
- The Array  
Of Microarray Users
- White Knights  
Of Industry

1) How would you define a financial conflict of interest in clinical research, and how would you deal with it?

2) What volunteer activities have proved most rewarding for you? What volunteer activities would you encourage early-career scientists to pursue?

3) What sorts of professional or personal disputes at the NIH workplace have you encountered that would have benefited from ombudsman avenues of resolution?

4) Retirement, anyone?

The *NIH Catalyst* is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 2, Room 2W23, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: <catalyst@nih.gov>

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